

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/077920 A1

(51) International Patent Classification⁷: **A61K 31/5025**,
9/14, 47/38, 47/10, 47/20, A61P 29/00

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(21) International Application Number: PCT/EP03/02698

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(22) International Filing Date: 13 March 2003 (13.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0206200.8 15 March 2002 (15.03.2002) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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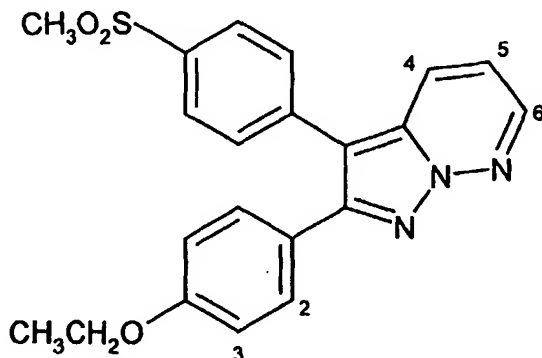
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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING 2-(4-ETHOXY-PHENYL)-3-(4-METHANESUL-
FONYL-PHENYL)-PYRAZOLO-1,5-BIPYRIDAZINE IN NANOPARTICULATE FORM



(I)

(57) Abstract: The invention provides a
pharmaceutical composition comprising a
compound of formula (I) and pharmaceu-
tically acceptable salts thereof, in which
the compound is present in solid particles
in nanoparticulate form, in admixture with
one or more pharmaceutically acceptable
carriers or excipients.

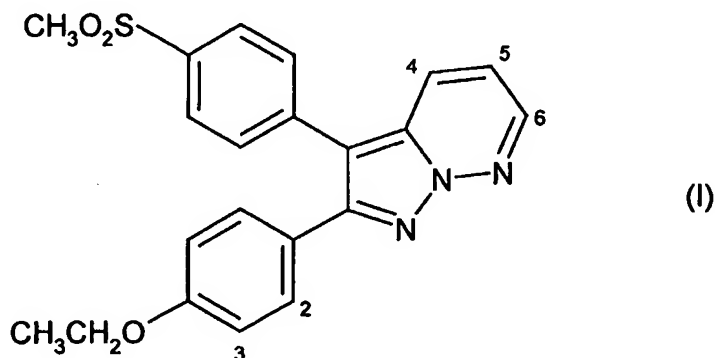
WO 03/077920 A1

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PHARMACEUTICAL COMPOSITIONS COMPRISING 2-(4-ETHOXY-PHENYL)-3-(4-METHANESULFONYL-PHENYL)-PYRAZOLO[1,5-b]PYRIDAZINE IN NANOPARTICULATE FORM

The present invention relates to certain novel pharmaceutical compositions comprising a selective cyclooxygenase-2 inhibitor, processes for their preparation, methods of treatment of cyclooxygenase-2 mediated diseases comprising administering such compositions to a subject, and to the use of such compositions in the manufacture of medicaments.

WO99/12930 (Glaxo Group Limited) discloses 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (I) as a potent and selective inhibitor of cyclooxygenase-2 (COX-2).



Dissolution testing is a well established technique for obtaining a correlation between in vitro and in vivo data in relation to compound bioavailability. Preliminary dissolution experiments employing compound (I) in micronised form predicted it to be poorly bioavailable. As a result attempts were made to improve the bioavailability of compound (I). WO01/41760 (Pharmacia Corporation) discloses that the bioavailability of selective COX-2 inhibitory drugs of low water solubility may be enhanced by reducing the drug particle size, such that a substantial proportion are smaller than 1 μm . However, dissolution experiments using a pharmaceutical composition comprising compound (I), wherein the drug was present in nanoparticulate form, still resulted in a poor dissolution profile, thus predicting this pharmaceutical composition to be poorly bioavailable in man. Further dissolution experiments indicated that the bioavailability of compound (I) could be enhanced by co-formulation with hydroxypropylmethylcellulose-acetyl succinate (HPMC-AS) in an amorphous dispersion. Moreover a 1:1 ratio of compound (I) and HPMC-AS was found to be optimal.

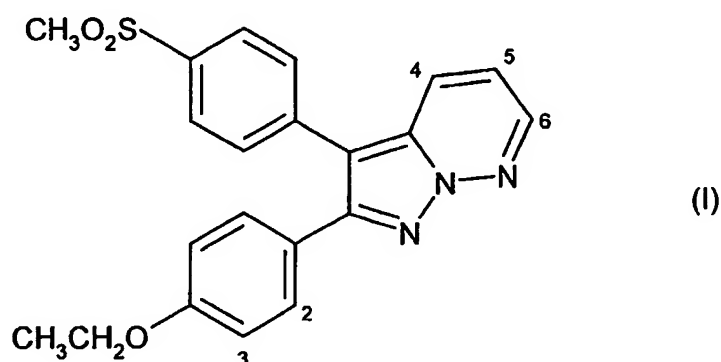
As a result a pharmaceutical composition comprising a 1:1 ratio of compound (I) and hydroxypropylmethylcellulose-acetyl succinate (HPMC-AS) as an amorphous dispersion has been administered to man at 35mg o.d. The resulting pharmacokinetic parameters such as the maximum blood serum concentration of the drug (C_{max}), the time to achieve the maximum

blood serum concentration of the drug (T_{max}) and the exposure of the volunteer to the drug as measured by the area under the plasma concentration versus time curve (AUC) were all conducive to the further development of compound (I). However, unacceptably high inter-subject variability was seen for these parameters.

5

The problem of high inter-subject variability for the parameters C_{max} , T_{max} and AUC may be solved by providing a pharmaceutical composition comprising compound (I), wherein the drug is present in nanoparticulate form.

- 10 Accordingly, in a first aspect the invention thus provides a pharmaceutical composition comprising a compound of formula (I)



- 15 and pharmaceutically acceptable salts thereof, in which the compound is present in solid particles in nanoparticulate form, in admixture with one or more pharmaceutically acceptable carriers or excipients.

- Surprisingly, we have now found that a pharmaceutical composition as defined hereinabove results in significantly reduced inter-subject variability for both C_{max} , T_{max} and AUC when
20 dosed in human volunteers. Furthermore, and contrary to expectation, this pharmaceutical composition resulted in a pharmacokinetic profile in man with a shorter T_{max} , a higher C_{max} and a higher AUC in comparison with the pharmacokinetic profile for the composition comprising a 1:1 ratio of compound (I) and hydroxypropylmethylcellulose-acetyl succinate (HPMC-AS) as an amorphous dispersion. Such a pharmacokinetic profile is particularly
25 beneficial for the treatment of acute pain disorders where early and rapid relief from the pain or other symptoms is desired.

For the purposes of the present invention "nanoparticulate" is defined as solid particles with a median size by volume $[D(v,0.5)]$ in the range 0.4 to 1.8 μm .

30

In another aspect of the invention compound (I) is present in solid particles with a $D(v,0.5)$ in the range 0.4 to 1.5 μm .

5 In another aspect of the invention compound (I) is present in solid particles with a $D(v,0.5)$ in the range 0.45 to 1.05 μm .

In another aspect of the invention compound (I) is present in solid particles with a $D(v,0.5)$ of 0.8 μm .

10 The particle size of the solid particles of compound (I) may be determined by laser diffraction. A suitable machine for determining particle size by laser diffraction is a Sympatec laser diffraction unit, using an HELOS optical bench fitted with a QUIXEL dispersion unit. As used herein, the median size by volume [$D(v,0.5)$] of the particles is determined by laser diffraction, as defined above.

15 Numerous processes for the synthesis of solid particles in nanoparticulate form are known. Typically these processes involve a milling process, preferably a wet milling process in the presence of a surface modifying agent that inhibits aggregation and/or crystal growth of the nanoparticles once created. Alternatively these processes may involve a precipitation process,
20 preferably a process of precipitation in an aqueous medium from a solution of the drug in a non-aqueous solvent.

Accordingly, in a further aspect, the present invention provides a process for preparing compound (I) in nanoparticulate form as hereinbefore defined, which process comprises milling
25 or precipitation.

Representative processes for the preparation of solid particles in nanoparticulate form are described in the patents and publications listed below.

U.S. Patent No. 4,826,689 to Violanto & Fischer

30 U. S. Patent No. 5,145,684 to Liversidge et al

U.S. Patent No. 5,298,262 to Na & Rajagopalan

U.S. Patent No. 5,302,401 Liversidge et al

U.S. Patent No. 5,336,507 to Na & Rajagopalan

U.S. Patent No. 5,340,564 to Illig & Sarpotdar

35 U.S. Patent No. 5,346,702 to Na Rajagopalan

U.S. Patent No. 5,352,459 to Hollister et al

U.S. Patent No. 5,354,560 to Lovrecich

- U.S. Patent No. 5,384,124 to Courteille et al
U.S. Patent No. 5,429,824 to June
U.S. Patent No. 5,503,723 to Ruddy et al
U.S. Patent No. 5,510 118 to Bosch et al
- 5 U.S. Patent No. 5,518 to Bruno et al
U.S. Patent No. 5,518,738 to Eickhoff et al
U.S. Patent No. 5,534,270 to De Castro
U.S. Patent No. 5,536,508 to Canal et al
U.S. Patent No. 5,552,160 to Liversidge et al
- 10 U.S. Patent No. 5,560,931 to Eickhoff et al
U.S. Patent No. 5,560,932 to Bagchi et al
U.S. Patent No. 5,565,188 to Wong et al
U.S. Patent No. 5,571,536 to Eickhoff et al
U.S. Patent No. 5,573,783 to Desieno & Stetsko
- 15 U.S. Patent No. 5,580,579 to Ruddy et al
U.S. Patent No 5,585,108 to Ruddy et al
U.S. Patent No. 5,587,143 to Wong
U.S. Patent No. 5,591,456 to Franson et al
U.S. Patent No. 5,622,938 to Wong
- 20 U.S. Patent No 5,662,883 to Bagchi et al
U.S. Patent No. 5,665,331 to Bagchi et al
U.S. Patent No. 5,718,919 to Ruddy et al
U.S. Patent No. 5,747,001 to Wiedmann et al
International Patent Publication No WO93/25190
- 25 International Patent Publication No. WO96/24336
International Patent Publication No. WO 97/14407
International Patent Publication No. WO 98/35666
International Patent Publication No. WO 99/65469
International Patent Publication No. WO 00/18374
- 30 International Patent Publication No. WO 00/27369
International Patent Publication No. WO 00/30615 and
International Patent Publication No. WO 01/41760.

Such processes may be readily adapted for the preparation of compound (I) in nanoparticulate
35 form. Such processes form a further aspect of the invention.

The process of the present invention preferably uses a wet milling step carried out in a mill such as a dispersion mill in order to produce a nanoparticulate form of the compound. The present invention may be put into practice using a conventional wet milling technique, such as that described in Lachman *et al.*, The Theory and Practice of Industrial Pharmacy, Chapter 2, "Milling" p.45 (1986).

In a further refinement, PCT/EP01/07085 (SmithKline Beecham plc) describes a wet milling procedure using a mill in which at least some of the surfaces are made of nylon (polyamide) comprising one or more internal lubricants, for use in the preparation of solid particles of a drug substance in nanoparticulate form.

In another aspect the present invention provides a process for preparing compound (I) in nanoparticulate form comprising wet milling a suspension of compound (I) in a mill having at least one chamber and agitation means, said chamber(s) and/or said agitation means comprising a lubricated nylon, as described in PCT/EP01/07085.

The suspension of compound (I) for use in the wet milling is typically a liquid suspension of the coarse compound in a liquid medium. By "suspension" is meant that the compound is essentially insoluble in the liquid medium. Representative liquid media include an aqueous medium. Using the process of the present invention the average particle size of coarse compound (I) may be up to 1mm in diameter. This advantageously avoids the need to pre-process the compound.

In a further aspect of the invention the aqueous medium to be subjected to the milling comprises compound (I) present in from about 1% to about 40% w/w, preferably from about 10% to about 30% w/w, more preferably about 20% w/w.

The aqueous medium may further comprise one or more pharmaceutically acceptable water-soluble carriers which are suitable for steric stabilisation and the subsequent processing of compound (I) after milling to a pharmaceutical composition, e.g. by spray drying.

Pharmaceutically acceptable excipients most suitable for steric stabilisation and spray-drying are surfactants such as poloxamers, sodium lauryl sulphate and polysorbates etc; stabilisers such as celluloses e.g. hydroxypropylmethyl cellulose; and carriers such as carbohydrates e.g. mannitol.

In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise hydroxypropylmethyl cellulose (HPMC) present in from about 0.1 to about 10% w/w, preferably in about 5% w/w in the aqueous medium to be subjected to the milling.

In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise hydroxypropylmethyl cellulose (HPMC) present in about 3% w/w or 1% w/w.

5 In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise mannitol present in from about 1 to about 15% w/w, preferably in about 10% w/w, in the aqueous medium to be subjected to the milling.

10 In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise sodium lauryl sulphate present in about 0.2% w/w.

The process of the present invention may comprise the subsequent step of drying compound (I) to yield a powder.

15 Accordingly, in a further aspect, the present invention provides a process for preparing a pharmaceutical composition as hereinbefore defined, which process comprises producing compound (I) in nanoparticulate form optionally followed by drying to yield a powder.

20 By "drying" is meant the removal of any water or other liquid vehicle used during the process to keep compound (I) in liquid suspension or solution. This drying step may be any process for drying known in the art, including freeze drying, spray granulation or spray drying. Of these methods spray drying is particularly preferred. All of these techniques are well known in the art. Spray drying/fluid bed granulation of milled compositions is carried out most suitably using a spray dryer such as a Mobile Minor Spray Dryer [Niro, Denmark], or a fluid bed drier, such as those manufactured by Glatt, Germany.

25 In a further aspect the invention provides a pharmaceutical composition as hereinbefore defined, in the form of a dried powder, obtainable by wet milling solid particles of compound (I) followed by spray-drying the resultant suspension.

30 Preferably, the pharmaceutical composition as hereinbefore defined, further comprises HPMC present in less than 15% w/w, preferably in the range 0.1 to 10% w/w, more preferably in about 5% w/w.

35 Preferably, the pharmaceutical composition as hereinbefore defined, further comprises HPMC present in about 3% w/w or 8% w/w.

Preferably the pharmaceutical composition as hereinbefore defined, in the form of a dried powder, further comprises mannitol present in less than 30% w/w, preferably in the range 1 to 15% w/w, more preferably in about 10% w/w.

- 5 Preferably, the pharmaceutical composition as hereinbefore defined, in the form of a dried powder, further comprises mannitol present in the range 30 to 45% w/w, more preferably in about 34% w/w or 43% w/w.

- 10 Preferably, the pharmaceutical composition as hereinbefore defined, in the form of a dried powder, further comprises sodium lauryl sulphate present in about 0.6% w/w.

Preferably the pharmaceutical composition as hereinbefore defined, in the form of a dried powder, further comprises HPMC present in less than 15% w/w, preferably in the range 0.1 to 10% w/w, and mannitol present in less than 30% w/w, preferably in the range 1 to 15% w/w.

- 15 Preferably the pharmaceutical composition as hereinbefore defined, in the form of a dried powder, further comprises HPMC present in about 3% w/w, mannitol present in the range 30 to 45% w/w, more preferably in about 34% w/w, and sodium lauryl sulphate present in about 0.6% w/w.

- 20 The solid particles of compound (I) obtainable by wet milling, optionally followed by the step of spray-drying, according to the present invention, may be presented in a variety of finished formulations including, for instance, tablets, for example swallow tablets, dispersible tablets and chewable tablets; in capsules; aqueous syrups and sachets. These may be prepared by combining the pharmaceutical composition of the present invention with excipients conventionally used in such formulations such as disintegrants, diluents, lubricants, wetting agents, binding agents, flavoring agents, sweeteners, colouring agents, preservatives, suspending agents, coating agents and fillers, and further processing into finished formulations. Thus, in a further aspect, pharmaceutical formulations of the present invention comprise pharmaceutical compositions as hereinbefore defined, optionally together with one or more excipients such as disintegrants, diluents, lubricants, wetting agents, binding agents, flavoring agents, sweeteners, colouring agents, preservatives, suspending agents, coating agents and fillers.

- 35 Representative disintegrants for use in the instant invention illustratively include maize-starch and rice starch, cross-linked N-vinyl-2-pyrrolidinone, sodium starch glycollate, croscarmellose sodium, microcrystalline or microfine cellulose, low substituted hydroxypropylcellulose (i.e.

cellulose partially substituted with 2-hydroxypropyl groups e.g. less than 25% substituted) cross-linked sodium carboxymethylcellulose, swellable ion exchange resins, formaldehyde-casein or alignates.

- 5 Representative lubricants for use in the instant invention illustratively include a long chain fatty acid, such as stearic acid, or salts thereof, such as magnesium stearate.

Representative fillers for use in the instant invention illustratively include silicon dioxide, microcrystalline cellulose, dicalcium phosphate, lactose, sorbitol, calcium carbonate or
10 magnesium carbonate.

In another aspect the invention provides a pharmaceutical composition comprising compound (I) in a form which results in a pharmacokinetic profile in a healthy male volunteer study wherein the median T_{max} is in the range 0.75 to 1.25 hours, the median C_{max} is in the range 130 to
15 170 ng/mL and the AUC (last) is in the range 800 to 900 ng/mL.h.

In another aspect the invention is directed to a method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering a pharmaceutical composition comprising compound formula (I) or a pharmaceutically acceptable
20 salt thereof in which the compound is present in solid particles in nanoparticulate form.

In another aspect the invention is directed to the use of a pharmaceutical composition comprising compound (I) or a pharmaceutically acceptable salt thereof in which the compound is present in solid particles in nanoparticulate form for the manufacture of a medicament for the
25 treatment of a condition which is mediated by COX-2.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by
30 reference herein as being fully set forth.

The example that follows illustrates the invention but does not limit the invention in any way.

Example 1 (Pharmaceutical Composition 2)

35 A 1 kg batch of an aqueous suspension containing 20% w/w of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine and 5% w/w of hydroxypropylmethylcellulose was passed through a Dena DM-100 bead mill. The single 100ml chamber fabricated from

Nylacast Nylube was used in a recirculation configuration with the chamber containing 85% by volume of yttrium stabilised zirconium oxide beads (Tosoh, Japan). The batch was processed using four different bead sizes in sequence: 1mm diameter bead sample, 0.65mm diameter bead sample, 0.4mm diameter bead sample, 0.3mm diameter bead sample. The batch was processed for one hour using each bead sample. The yield was 81.3%. To the finely milled suspension was added 10% w/w mannitol and the resulting suspension subsequently spray-dried to yield Pharmaceutical Composition 2.

Grinding media contamination levels in the spray-dried powder (Pharmaceutical Composition 2) were 7ppm zirconium (Zr) and <1ppm yttrium (Y).

The product had a median particle size of 1.01 microns as measured by laser diffraction size analysis using a Sympatec laser diffraction unit, with a HELOS optical bench fitted with a QUIXEL dispersion unit.

Example 2

A 5 kg batch of an aqueous suspension containing 20% w/w of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine, 0.2% w/w of sodium lauryl sulphate and 1% w/w of hydroxypropylmethylcellulose was passed through a Drais Cosmo 5 bead mill. The single 500ml chamber fabricated from Sustaplast Nylon 6G was used in a recirculation configuration with the chamber containing 570 mL of yttrium stabilised zirconium oxide beads (Tosoh, Japan). The batch was processed using two different bead sizes in sequence: 0.8 mm diameter bead sample and a 0.3 mm diameter bead sample. The batch was processed for 23 minutes for the larger bead size and 80 minutes for the smaller bead size. The yield was 90%. To the finely milled suspension was added 10% w/w mannitol and the resulting suspension subsequently spray-dried to yield Example 2.

The product had a median particle size of 0.8 microns as measured by laser diffraction size analysis using a Sympatec laser diffraction unit, with a HELOS optical bench fitted with a QUIXEL dispersion unit.

Study 1

A randomised, open label, crossover comparison between single oral doses of 35mg of each of two pharmaceutical compositions of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine was conducted in 24 healthy male volunteers. Single oral doses of 35mg of each of two pharmaceutical compositions of 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine were administered to fasted volunteers. Seven day intervals

separated each dose. The pharmacokinetic characteristics of each pharmaceutical composition were determined over a 48 hour time period.

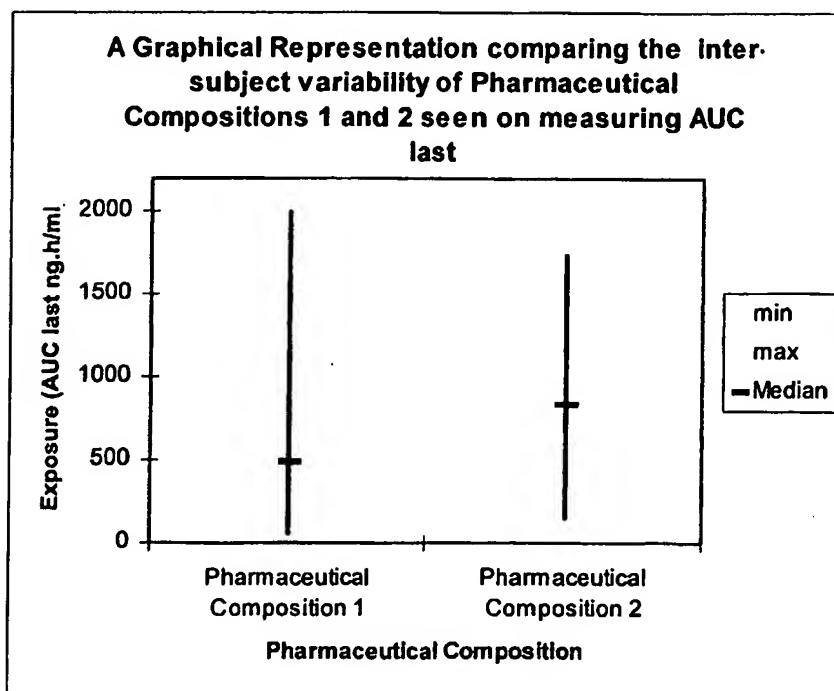
Pharmaceutical Composition 1 – Amorphous spray-dried pharmaceutical composition comprising 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine and hydroxypropylmethylcellulose-acetyl succinate in a 1:1 ratio produced by conventional spray-drying techniques.

Pharmaceutical Composition 2 – as for Example 1 above

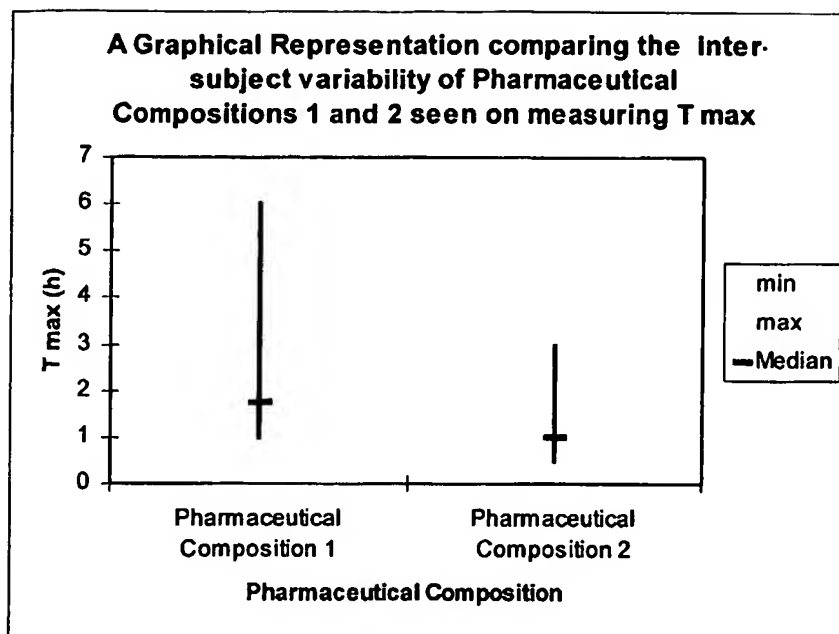
Table 1: Summary of Median Serum Derived Pharmacokinetic Parameters for Pharmaceutical Compositions 1 and 2 of 2-(4-Ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine from a Healthy Male Volunteer Study of 24 Subjects.

	AUC last (ng/mL.h)	T _{max} (h)	C _{max} (ng/mL)
Pharmaceutical Composition 1	492.16	1.75	72.39
Pharmaceutical Composition 2	840.13	1	152.33

Graph 1:

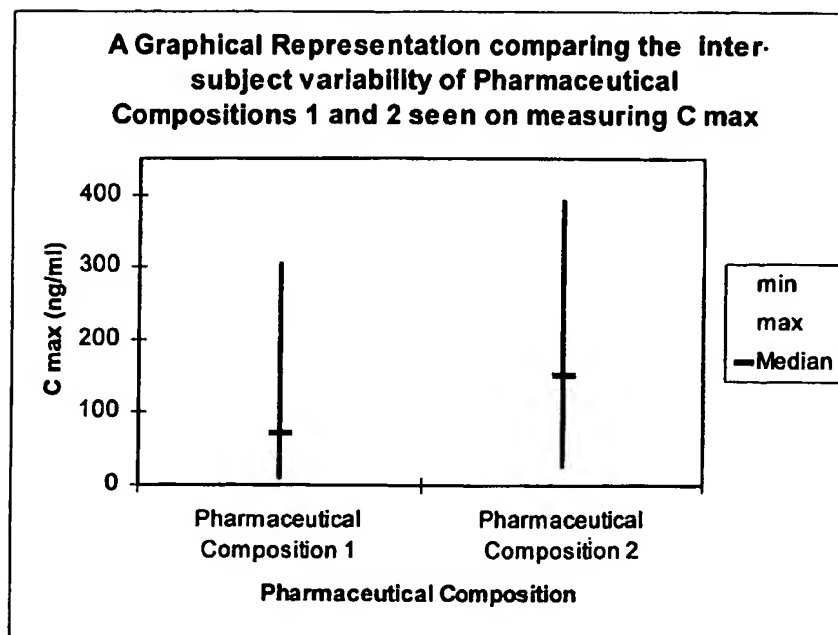


5 Graph 2:



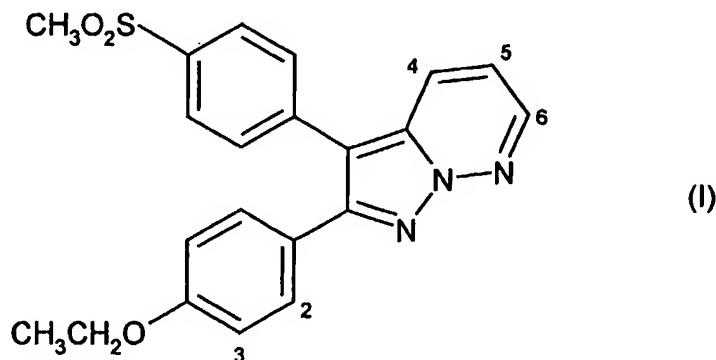
Graph 3:

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Claims

- 5 1. A pharmaceutical composition comprising compound (I)



and pharmaceutically acceptable salts thereof, in which the compound is present in solid particles in nanoparticulate form in admixture with one or more pharmaceutically acceptable carriers or excipients.

10

2. A pharmaceutical composition as claimed in claim 1 which further comprises HPMC present in less than 15% w/w.

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3. A pharmaceutical composition as claimed in claim 1 or claim 2 which further comprises mannitol present in the range 30 to 45% w/w.

4. A pharmaceutical composition as claimed in any of claims 1 to 3 which further comprises sodium lauryl sulphate present in about 0.6% w/w.

20

5. A process for preparing a pharmaceutical composition according to any of claims 1 to 4 comprising wet milling a suspension of compound (I) in a mill having at least one chamber and agitation means, said chamber(s) and/or said agitation means comprising a lubricated nylon.

25

4. A method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering a pharmaceutical composition as defined in any of claims 1 to 4.

5. The use of a pharmaceutical composition as defined in any of claims 1 to 4 for the manufacture of a medicament for the treatment of a condition which is mediated by COX-2.

INTERNATIONAL SEARCH REPORT

PCT/EP 03/02698

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5025 A61K9/14 A61K47/38 A61K47/10 A61K47/20
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 01 41760 A (HAGEMAN MICHAEL J ;DESAI SUBHASH (US); KONTRY MARK J (US); HASKELL) 14 June 2001 (2001-06-14) cited in the application page 3, line 7 -page 6, line 31 page 7, line 14 -page 8, line 18 page 9, line 26 -page 12, line 8 page 16, line 2 page 17, paragraph 3 page 26, line 17 -page 27, line 4 page 30, line 9 - line 16 page 31, line 12 - line 23 page 34, line 28 page 37, line 5 page 37, line 12 - line 15 page 43, line 11 -page 44, line 26 claims 1,3,8-10,16</p> <p style="text-align: center;">--- -/--</p>	1-7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 May 2003

Date of mailing of the international search report

13/05/2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

PCT/EP 03/02698

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 00196 A (KNIGHT WENDY ANNE ;HOLLAND SIMON JOSEPH (GB); LEONARD GRAHAM STANL) 3 January 2002 (2002-01-03) cited in the application the whole document examples 1,2 -----	1-7

INTERNATIONAL SEARCH REPORT

PCT/EP 03/02698

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0141760	A	14-06-2001	AU 1805901 A	18-06-2001
			AU 1930301 A	18-06-2001
			AU 1931001 A	18-06-2001
			AU 1931101 A	18-06-2001
			AU 2041201 A	18-06-2001
			AU 750978 B2	01-08-2002
			AU 2057101 A	18-06-2001
			BG 105808 A	30-09-2002
			BG 105873 A	30-04-2002
			BR 0008058 A	26-03-2002
			BR 0008059 A	26-03-2002
			BR 0008060 A	05-02-2002
			BR 0008088 A	09-04-2002
			CA 2362673 A1	14-06-2001
			CA 2362675 A1	14-06-2001
			CN 1376146 T	23-10-2002
			CN 1379669 T	13-11-2002
			CZ 20012875 A3	13-02-2002
			CZ 20013162 A3	12-06-2002
			CZ 20013163 A3	12-06-2002
			CZ 20013210 A3	13-03-2002
			EE 200100414 A	16-12-2002
			EE 200100419 A	16-12-2002
			EP 1175214 A2	30-01-2002
			EP 1165072 A2	02-01-2002
			EP 1150959 A1	07-11-2001
			EP 1150960 A1	07-11-2001
			HR 20010582 A1	31-08-2002
			HR 20010589 A1	31-08-2002
			HU 0200409 A2	29-06-2002
			HU 0200580 A2	28-11-2002
			HU 0201450 A2	28-12-2002
			NO 20013855 A	05-10-2001
			NO 20013858 A	08-10-2001
			NO 20013859 A	08-10-2001
			NO 20013868 A	03-10-2001
			NZ 513960 A	28-09-2001
			NZ 513963 A	28-09-2001
			NZ 513964 A	28-09-2001
			NZ 514059 A	28-09-2001
			PL 349223 A1	01-07-2002
			PL 349224 A1	01-07-2002
			SK 11522001 A3	09-05-2002
			SK 12672001 A3	04-04-2002
			SK 12682001 A3	02-07-2002
			SK 12692001 A3	04-04-2002
			TR 200102297 T1	21-03-2002
WO 0200196	A	03-01-2002	AU 1560802 A	08-01-2002
			WO 0200196 A2	03-01-2002
			EP 1294358 A2	26-03-2003
			NO 20026120 A	27-01-2003